2.C. ***Request for data on combination products to establish general recognition of safety and effectiveness***

The Subcommittee applied the regulation cited in 21CFR§330.10(4)(iv) for OTC Combination Products when considering general recognition of safety and effectiveness for combination products containing an antigingivitis or antigingivitis/antiplaque active ingredient:

> *"An OTC drug may combine two or more safe and effective active ingredients, and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety and effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."*

On November 28, 1978 [Docket No. 76D-0322], the FDA announced the availability of a guideline that states in detail the policy for combining two or more safe and effective over-the-counter active ingredients. In this announcement, FDA stated that the regulatory requirements for OTC combination drug products are sufficiently general. The OTC drug Review Panels "were encouraged to exercise their own scientific judgment in developing all aspects of their reports".[18] Through their recommendations the Plaque Subcommittee affirmatively endorsed FDA's combination policy.

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[18] Federal Register 43 (55463); November 28, 1978

Using this regulation and similar principles listed in the Panel Report, the Subcommittee concluded that combining a Category I antigingivitis or antigingivitis/antiplaque ingredient with an anticaries and/or tooth desensitizer active ingredient represented rational combinations that could be marketed as safe and effective under the ANPR. However, the Agency dissented from this position on the basis that they were "*not aware of any marketing history of such combination products eligible for the OTC drug review, nor were such combinations submitted to the Subcommittee*,"[19] and specified that no active ingredient combination product could be marketed under the ANPR. We respectfully disagree with the Agency's decision on this matter and request their reconsideration for the following reasons:

- the Subcommittee's recommendation for combination products meets the OTC Combination regulations and policies in all respects (330.10(4)(iv)).
- the **OTC Antigingivitis/Antiplaque Proposed Monograph** has performance standards that are used to ensure the activity of the antigingivitis/antiplaque active ingredient is not compromised in the presence of numerous types of formulation components, including anticaries active ingredients.
- the **OTC Anticaries Final Monograph** has well-established performance standards that are used to ensure the activity of the anticaries active ingredient is not compromised in the presence of numerous types of formulation components, including antigingivitis/antiplaque active ingredients. Further, the Agency has previously agreed with the utility of these performance tests and has stated, "*the LTP's (Laboratory Tests for Performance) could be used to demonstrate the anticaries effectiveness of the fluoride in any combination*

[19] Federal Register. 68(103) p.32232, May 29, 2003

dentifrice containing 5 percent potassium nitrate and a Category I fluoride ingredient."[20]

- throughout the OTC Review there are numerous precedent examples of many types of permitted OTC combinations, including among others: four-way cough/cold products containing pain relievers, nasal decongestants, cough suppressants and antihistamines; internal analgesics containing two pain relievers and an analgesic adjuvant; combinations of three sunscreens or a sunscreen and a skin protectant; ophthalmic combinations containing a variety of ingredients from the same and different pharmacologic class. In each case, FDA determined that the combination was rational, the actives contributed to the claimed effect(s), and the combination of the ingredients did not interfere with the safety or effectiveness of any of the ingredients, per the longstanding OTC review combination policy.

- the dissention is contrary to the September 2000 Surgeon General's report on Oral Health in America[21] which cites rampant oral disease in the US population and its potential link with systemic diseases. The need for oral health care products with multiple pharmacologic activities, as would be possible through the combinations recommended by the Subcommittee, would help address this deficit in US oral health.

- the dissention may result in consumer confusion, and importantly to lack of caries prevention, in cases where new antigingivitis/antiplaque dentifrice drug products are introduced to the market under this monograph, but which could not contain a fluoride ingredient because of the Agency's position on combination products. Quantitative Consumer Research[22] (n=1225) conducted

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[20] Federal Register. 56: May 11, 1992 at page 48332.

[21] Website: http://www.nidcr.nih.gov/sgr/execsumm.htm

[22] Procter & Gamble Consumer Research – data on file

by Procter & Gamble shows that the overwhelming majority (>93 %) of consumers expect a dentifrice to provide cavity protection.

- some antigingivitis active ingredients reviewed under the call for data were actually marketed in formulations combined with other active ingredients prior to the call-for-data. According to the Panel Report, the following products were submitted for review by the Plaque Subcommittee: Mentadent® P Toothpaste; Arm & Hammer® Dental Care Toothpaste, Arm & Hammer® Dental Care Toothpowder and Viadent® Toothpaste. As such, these products represented antiplaque/antigingivitis and anticaries dentifrice products that were evaluated for safety and antiplaque/antigingivitis efficacy. Furthermore, for the rinse products, clinical evaluations included brushing with a fluoridated dentifrice immediate prior to oral rinsing.

- the Agency has previously allowed an oral care combination [5 percent potassium nitrate and Category I anticaries fluoride] to be marketed that had not been previously reviewed by an OTC advisory panel. In this example, marketing of the combination was permitted via publication of an enforcement policy issued from the Commissioner's office and published in the Federal Register.[23]

All considered, we recommend that combination products containing an anticaries fluoride ingredient, a Category I antigingivitis/antiplaque ingredient and/or a tooth desensitizer ingredient should be allowed to be marketed during this rulemaking process. There are suitable performance tests in two of these monographs to assure the effectiveness of each active ingredient in the combination and each active ingredient makes a contribution to the claimed effect(s) and the combination represents rational concurrent therapy for a significant proportion of the target population.

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[23] Federal Register. 57 : May 11, 1992 at page 20114.

Additionally, in contradistinction to combination products discussed above where more than one active ingredient is combined in a single formulation, it should be noted that stannous fluoride is a single ingredient with multiple activities recognized by three different monographs. These monographs include:

1. SnF_2 is a recommended Category I antigingivitis agent in the OTC Antigingivitis/Antiplaque Advanced Notice of Proposed Rulemaking[24]
2. SnF_2 is a recognized anticaries agent in the OTC Anticaries Final Monograph[25], and
3. SnF_2 is a Category III tooth-desensitizing agent in the OTC Tentative Final Monograph for Relief of Oral Discomfort[26].

It is noteworthy that there are several active ingredients on the market, like stannous fluoride, which have multiple activities that are covered under different OTC monographs. One such examples is bismuth subsalicylate which is an antidiarrheal active and an overindulgence active ingredient. OTC products containing this active ingredient carry labeling for both uses on the same label. In this case, as with other active ingredients having multiple activities covered under multiple monographs, the Agency has been diligent in ensuring that labeling provides consistent information across the monographs to avoid consumer confusion in regards to the multiple uses of these products.

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[24] Federal Register. 68 (103): May 29, 2003 at page 32285.

[25] 21 CFR Part 355

[26] Federal Register. 56: September 24, 1991, p 48302-48347.